Chapter 14
The Burst Mode of the Mutant Sodium Channel

We observed above that the effect of the ΔKPQ mutation of the SCN5A gene leading to a delayed sodium current can be modeled by increasing the reaction rates from the inactivated state to the open state and to the permissible state C_0. The model gave results at least qualitatively similar to the experimental data (see Fig. 12.4).

A better-established way of modeling the effect of the mutation is to introduce a so-called burst mode. A simple Markov model including a burst mode is illustrated in Fig. 14.1, where the states of the burst mode are indicated by $*$. Note that when the channel is in the burst mode, there is no inactivated state and therefore the burst mode can be used to model the effect of impaired inactivation. The reaction rates going from the burst mode to the normal mode are given by k^u (where u stands for up) and the reaction rates from the normal mode to the burst mode are given by k^d (where d stands for down). We assume $k^d << k^u$, which means that, for the wild type, the probability of being in the burst mode is very small. The probability of being in the burst mode increases with the mutation severity index μ. As usual, $\mu = 1$ represents the wild type. In the wild type, a channel is basically never in the burst mode and therefore the channel inactivates as it should and no late sodium current is observed. In the mutant case, however, the probability of being in the burst mode is increased. Since there is no inactivated state in the burst mode, the channel fails to inactivate and therefore the probability of being in the open state is increased and therefore we observe a non-negligible late current. This will be illustrated in the numerical computations below.

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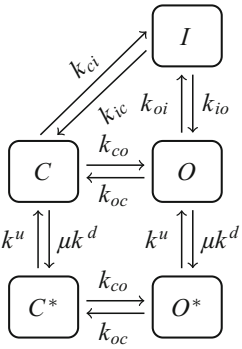

Fig. 14.1 Prototypical model of a sodium channel including a burst mode. The model consists of the states O, I, and C of the normal mode and O^* and C^* of the burst mode (*lower part*)

14.1 Equilibrium Probabilities

We will start by considering the equilibrium states of the prototypical model illustrated in Fig. 14.1. By following the usual steps (see, e.g., page 187) we find the equilibrium probabilities given by

$$o = \frac{1}{1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}\frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}}, \tag{14.1}$$

$$i = \frac{\frac{k_{oi}}{k_{io}}}{1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}\frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}}, \tag{14.2}$$

$$c = \frac{\frac{k_{oc}}{k_{co}}}{1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}\frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}}, \tag{14.3}$$

$$c^* = \frac{\frac{k_{oc}}{k_{co}}\frac{\mu k^d}{k^u}}{1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}\frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}}, \tag{14.4}$$

$$o^* = \frac{\frac{\mu k^d}{k^u}}{1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}\frac{k_{oc}}{k_{co}} + \frac{\mu k^d}{k^u}}. \tag{14.5}$$

Here, we observe that the equilibrium probability of being in the inactivated state is clearly reduced as the mutation severity index is increased. This is the effect we wanted, since inactivation is impaired in the mutation and the effect is modeled by introducing a burst mode that lacks the inactivated state. Second, we observe that the sum of the open probabilities given by

$$o + o^* = \frac{1 + \mu\frac{k^d}{k^u}}{1 + \frac{k_{oi}}{k_{io}} + \frac{k_{oc}}{k_{co}} + \mu\frac{k^d}{k^u}\frac{k_{oc}}{k_{co}} + \mu\frac{k^d}{k^u}} \tag{14.6}$$

is an increasing function of μ; in fact,

$$\frac{d}{d\mu}\left(o+o^*\right)=\frac{\frac{k^d}{k^u}\frac{k_{oi}}{k_{io}}}{\left(1+\frac{k_{oc}}{k_{co}}+\frac{k_{oi}}{k_{io}}+\mu\frac{k^d}{k^u}\frac{k_{oc}}{k_{co}}+\mu\frac{k^d}{k^u}\right)^2}>0. \tag{14.7}$$

So the model has the two main properties we seek: The equilibrium probability of being in the inactivated state is reduced and the open probability is increased.

14.2 The Mean Open Time

We observed above (see page 196) that the formula for the mean open time can also be derived in the presence of several open states. If we generalize the argument to also take into account the inactivated state, we find that the mean open time of the Markov model illustrated in Fig. 14.1 is given by

$$\tau_{o,\mu}=\frac{\mu k^d+k^u}{\mu k^d k_{oc}+k^u\left(k_{oc}+k_{oi}\right)} \tag{14.8}$$

and, since

$$\frac{d\tau_{o,\mu}}{d\mu}=\frac{k_{oi}k^d k^u}{\left(k^u k_{oc}+k^u k_{oi}+\mu k_{oc}k^d\right)^2}, \tag{14.9}$$

the mean open time increases as a function of the mutation severity index.

14.3 An Optimal Theoretical Open State Blocker

Our aim is now to define an open state drug that can repair both the equilibrium open probability and the mean open time. The structure of the open state blocker is given in Fig. 14.2 and the equilibrium total open probability is now given by

$$\left(o+o^*\right)_{\mu,d}=\frac{1+\mu\frac{k^d}{k^u}}{1+\frac{k_{oi}}{k_{io}}+\frac{k_{oc}}{k_{co}}+\mu\frac{k^d}{k^u}\frac{k_{oc}}{k_{co}}+\mu\frac{k^d}{k^u}+\frac{k_{ob}}{k_{bo}}\left(1+\frac{\mu k^d}{k^u}\right)}. \tag{14.10}$$

Furthermore, the mean open time is now given by

$$\tau_{o,\mu,d}=\frac{\mu k^d+k^u}{\mu k^d\left(k_{oc}+k_{ob}\right)+k^u\left(k_{oc}+k_{oi}+k_{ob}\right)}, \tag{14.11}$$

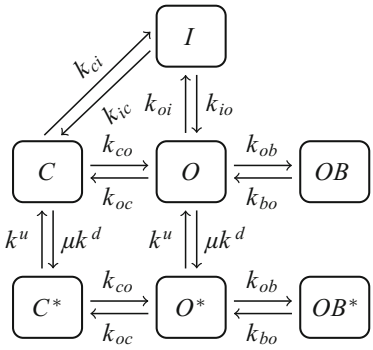

Fig. 14.2 Prototypical model of a sodium channel including a burst mode and an open state blocker. The model consists of the states O, I, C, and OB of the normal mode and O^*, C^*, and OB^* of the burst mode (*lower part*). The states OB and OB^* represent the open blocker and we assume that the rates characterizing the blocker are the same in the normal and burst modes

where the subscript d is used to remind us that this concerns the case where the theoretical drug has been applied.

The task at hand is now to tune the drug such that the equilibrium open probability and the mean open time given by (14.10) and (14.11), respectively, are as close as possible to the equilibrium open probability and the mean open time of the wild type. We regard the parameters k_{ob} and k_{bo} as the unknowns and we want to solve the following 2×2 system of equations:

$$\frac{1+\mu\frac{k^d}{k^u}}{1+\frac{k_{oi}}{k_{io}}+\frac{k_{oc}}{k_{co}}+\mu\frac{k^d}{k^u}\frac{k_{oc}}{k_{co}}+\mu\frac{k^d}{k^u}+\frac{k_{ob}}{k_{bo}}\left(1+\mu\frac{k^d}{k^u}\right)}=\frac{1+\frac{k^d}{k^u}}{1+\frac{k_{oi}}{k_{io}}+\frac{k_{oc}}{k_{co}}+\frac{k^d}{k^u}\frac{k_{oc}}{k_{co}}+\frac{k^d}{k^u}}, \tag{14.12}$$

$$\frac{\mu k^d+k^u}{\mu k^d\left(k_{oc}+k_{ob}\right)+k^u\left(k_{oc}+k_{oi}+k_{ob}\right)}=\frac{k^d+k^u}{k^d k_{oc}+k^u\left(k_{oc}+k_{oi}\right)}, \tag{14.13}$$

where the latter equation determines the on rate, k_{ob}, of the drug,

$$k_{ob}=(\mu-1)\frac{k^d k^u k_{oi}}{\left(k^u+\mu k^d\right)\left(k^u+k^d\right)}, \tag{14.14}$$

and we note that, in the case of $\mu = 1$, the drug is completely turned off, which is reasonable. Since k_{ob} is known, the off rate of the drug can be computed by solving (14.12). If we define

$$A=\frac{k_{ob}}{k_{bo}}, \tag{14.15}$$

we find from (14.12)

$$A = (\mu - 1)\frac{k_{oi}}{k_{io}}\frac{k^u k^d}{(\mu k^d + k^u)(k^d + k^u)} \tag{14.16}$$

and then the off rate of the drug is given by

$$k_{bo} = A^{-1}k_{ob} = k_{io} \tag{14.17}$$

which is the same as we have in the prototypical model given in Fig. 13.12; see (13.36) on page 217.

14.4 Numerical Experiments

The purpose of this section is to show how the burst mode can be used to represent impaired inactivation and how the theoretical drug derived above works.

14.4.1 Representation of the Late Sodium Current Using the Burst Mode Model

As discussed in Chap. 12, impaired inactivation leads to a late sodium current (see Fig. 12.4). Here, we will see that this effect can also be obtained using a Markov model of the form indicated in Fig. 14.1. In Fig. 14.3, we repeat the computations reported in Fig. 12.4, using the Markov model of Fig. 14.1. The parameters used in this computation are given in Table 14.1. We observe from Fig. 14.3 that $\mu = 20$ seems to represent the late current of Fig. 12.4 fairly well.

14.4.2 The Open State Blocker Repairs the Effect of the Mutation

In Fig. 14.3, we show the late current for the wild type, the mutant $\mu = 20$, and the drug using the optimal open state blocker defined by (14.14) and (14.17). We observe that the late current induced by the mutation is repaired by the open state blocker. The statistics of the open probability density function (for the wild type, the mutant ($\mu = 20$), and the mutant where the drug has been applied) are given in Table 14.2 and the corresponding probability density functions are shown in Fig. 14.4. Again we note that the open blocker repairs the main features of the solution.

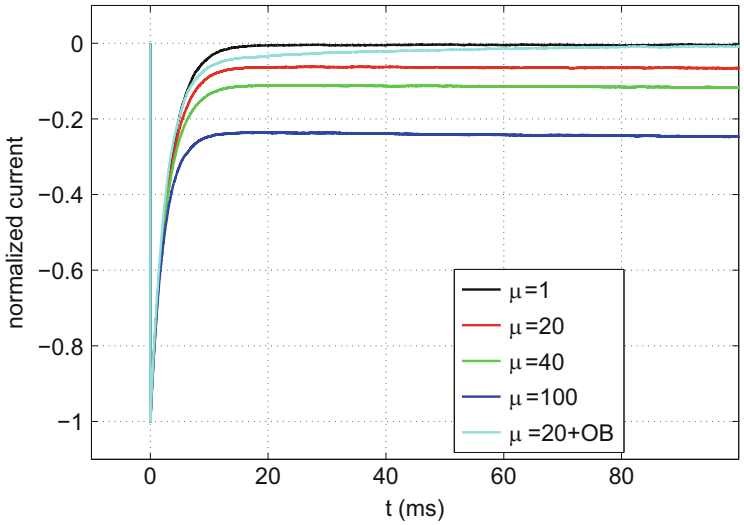

Fig. 14.3 Currents computed using the Markov model illustrated in Fig. 14.2. The simulations are based on averages of 10,000 runs. As expected, the open blocker asymptotically repairs the late current

Table 14.1 Values of the parameters used in the model in Fig. 14.2. The remaining rates are as in Table 12.2

μ	20
k_u	0.0001 ms^{-1}
k_d	0.001 ms^{-1}
k_{ob}	0.0286 ms^{-1}
k_{bo}	0.000824 ms^{-1}

Table 14.2 Statistics of the stationary probability density functions computed using the Markov model illustrated in Fig. 14.2. The subscript o refers to open states and the subscript n refers to non-conducting states

μ	π_o	π_n	E_o	E_n
1	0.59	0.41	31.2	−54.2
20	0.96	0.04	33.1	−52.8
50	0.98	0.02	33.1	−51.3
100	0.99	0.01	33.2	−49.8
20+OB	0.46	0.54	30.2	−57.9

14.5 A More Sophisticated Markov Model

The Markov model presented in Fig. 14.1 above has a structure that is a bit simpler than the Markov model commonly used to model the sodium channel. A more common structure is given in Fig. 14.5. This is the model we studied in Chap. 12. When a burst mode is added to it, the Markov model obtains the form illustrated in Fig. 14.6.

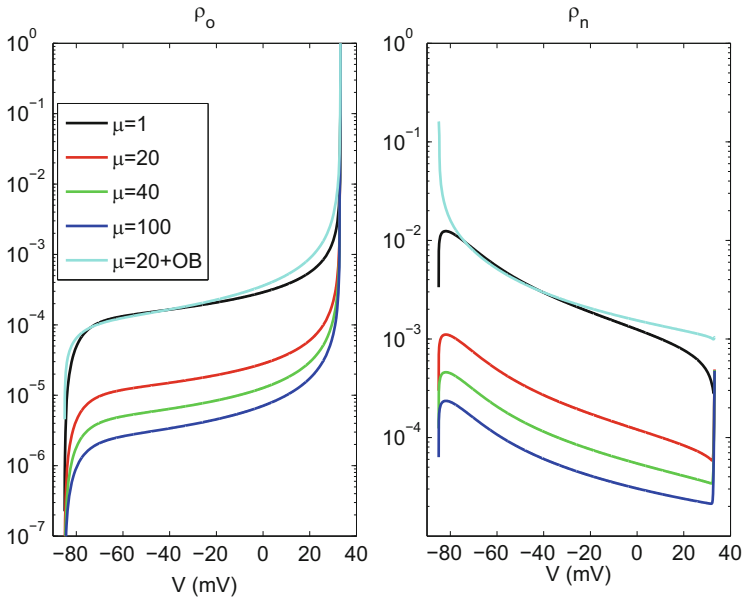

Fig. 14.4 Stationary probability density functions computed using the Markov model illustrated in Fig. 14.2. The open probability density function is given in the left panel and the probability density function of the sum of non-conducting states is given in the right panel. We observe that the open blocker repairs most parts of the probability density functions

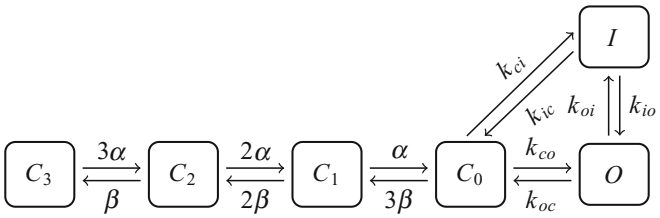

Fig. 14.5 Typical Markov model of a wild type sodium channel consisting of an open state (O), an inactivated state (I), and four closed states ($C_0, C_1, C_2,$ and C_3). This model was analyzed in Chap. 12

To understand how the burst mode changes the properties of the model, it is of interest to compute the equilibrium probabilities. The equilibrium state of the model presented in Fig. 14.6 is characterized by the following system of equations:

$$\begin{aligned} &k_{ci}c_0 = k_{ic}i, \quad k_{oi}o = k_{io}i, \quad k_{co}c_0 = k_{oc}o, \\ &3\beta c_0 = \alpha c_1, \quad 2\alpha c_2 = 2\beta c_1, \quad 3\alpha c_3 = \beta c_2, \\ &k^u o^* = \mu k^d o, \; k^u c_0^* = \mu k^d c_0, \; k^u c_1^* = \mu k^d c_1, \\ &k^u c_2^* = \mu k^d c_2, \; k^u c_3^* = \mu k^d c_3. \end{aligned} \tag{14.18}$$

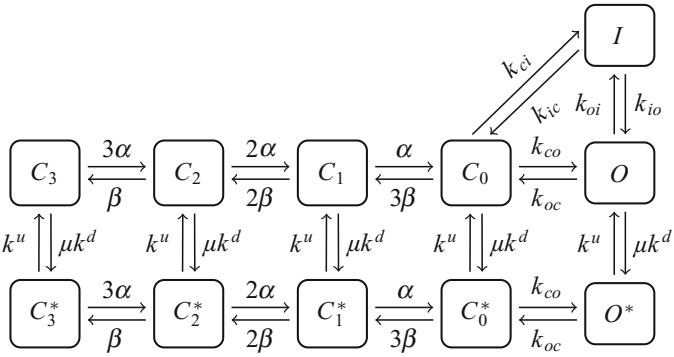

Fig. 14.6 Markov model of the sodium channel. The model consists of the states O, I, C_0, C_1, C_2, and C_3 of the normal mode and O^*, C_0^*, C_1^*, C_2^*, and C_3^* of the burst mode (*lower part*). Note that there is no inactivated state in the burst mode and that μ denotes the mutation severity index. A larger value of μ increases the probability of moving from the normal (*upper*) mode to the burst (*lower*) mode

It follows that

$$
\begin{aligned}
i &= \frac{k_{oi}}{k_{io}} o,\ c_0 = \frac{k_{oc}}{k_{co}} o, \\
c_1 &= \frac{3\beta}{\alpha} \frac{k_{oc}}{k_{co}} o,\ c_2 = \frac{3\beta^2}{\alpha^2} \frac{k_{oc}}{k_{co}} o,\ c_3 = \frac{\beta^3}{\alpha^3} \frac{k_{oc}}{k_{co}} o, \\
o^* &= \mu \frac{k^d}{k^u} o, c_0^* = \mu \frac{k^d}{k^u} \frac{k_{oc}}{k_{co}} o, c_1^* = \mu \frac{3\beta}{\alpha} \frac{k^d}{k^u} \frac{k_{oc}}{k_{co}} o, \\
c_2^* &= \mu \frac{3\beta^2}{\alpha^2} \frac{k^d}{k^u} \frac{k_{oc}}{k_{co}} o, c_3^* = \mu \frac{\beta^3}{\alpha^3} \frac{k^d}{k^u} \frac{k_{oc}}{k_{co}} o
\end{aligned}
$$

and, since the sum of the probabilities equals one, we have

$$
o(\mu) = \frac{1}{\frac{k_{oi}}{k_{io}} + \left(1 + \mu \frac{k^d}{k^u}\right) \left(1 + \frac{k_{oc}}{k_{co}} (1 + \beta/\alpha)^3\right)}
$$

and

$$
o(\mu) + o^*(\mu) = \frac{1 + \mu \frac{k^d}{k^u}}{\frac{k_{oi}}{k_{io}} + \left(1 + \mu \frac{k^d}{k^u}\right) \left(1 + \frac{k_{oc}}{k_{co}} (1 + \beta/\alpha)^3\right)}.
$$

Therefore,

$$\frac{d}{d\mu}\left(o\left(\mu\right)+o^{*}\left(\mu\right)\right)=\frac{\frac{k_{oi}}{k_{io}}\frac{k^{d}}{k^{u}}}{\left(\frac{k_{oi}}{k_{io}}+\left(1+\frac{k_{oc}}{k_{co}}\left(1+\beta/\alpha\right)^{3}\right)\left(1+\mu\frac{k^{d}}{k^{u}}\right)\right)^{2}}>0,$$

so the total open probability increases as the mutation severity index μ increases. This will lead to a sustained sodium current characteristic of the mutation under consideration.

It is also interesting to see how the mutation severity index changes the probability of being in the normal or burst mode. To understand this, we define b and b^{*} as the sum of the probabilities in the normal and burst modes, respectively. By using the equilibrium probabilities derived above, we obtain

$$\frac{b^{*}}{b}=\frac{o^{*}+c_{0}^{*}+c_{1}^{*}+c_{2}^{*}+c_{3}^{*}}{o+c_{0}+c_{1}+c_{2}+c_{3}+i}=\mu\frac{k^{d}}{k^{u}}\frac{1+\frac{k_{oc}}{k_{co}}\left(1+\beta/\alpha\right)^{3}}{\frac{k_{oi}}{k_{io}}+1+\frac{k_{oc}}{k_{co}}\left(1+\beta/\alpha\right)^{3}}$$

and thus the probability of being in the burst mode increases as the mutation severity index increases.

14.6 Numerical Experiments Illustrating the Effect of the Burst Mode

The effect of increasing the mutation severity index of the Markov model given in Fig. 14.6 is shown in Fig. 14.7 using the parameters given in Table 14.3. The associated currents are shown in Fig. 14.8 and we note that when the mutation severity index increases, there is a significant late sodium current (Table 14.4).

14.7 A Theoretical Drug for the Mutation Represented by the Burst Mode

In the simplified Markov model presented in Fig. 14.1 above, we saw that an open blocker was able to repair the effect of the mutation. Now the Markov model is extended (see Fig. 14.6), but it is reasonable to believe that an open blocker is still the best alternative, since both the open probability and the mean open time are affected by the mutation. We consider the Markov model given in Fig. 14.9, where

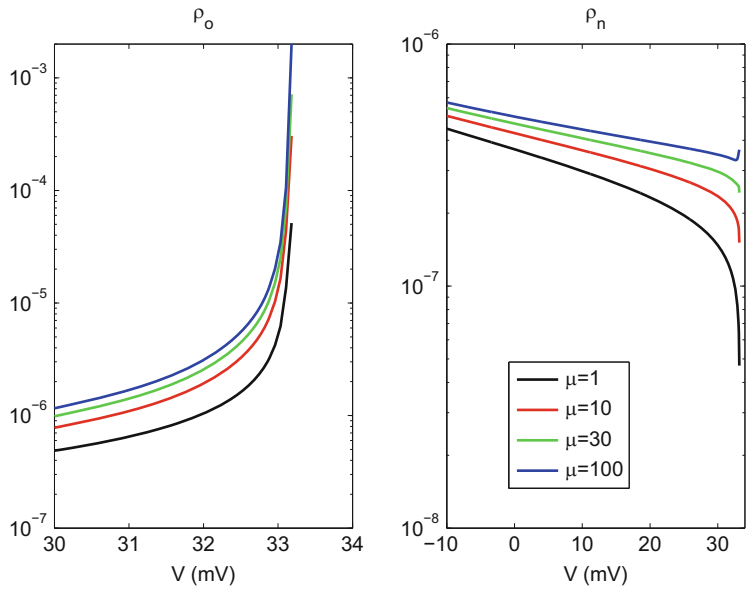

Fig. 14.7 The probability density functions of the open, closed, and inactivated states for the burst mode model. The mutation severity index is given by $\mu = 10,\ 30$, and 100 and the *black line* represents the wild type. Note that we only show solutions for the values of the transmembrane potential where the solutions differ as a result of the mutations

Table 14.3 Values of the parameters used in the model in Fig. 14.6. The remaining rates are as in Table 12.2 on page 184

μ	1,10,30,100
k_u	0.1 ms^{-1}
k_d	0.01 ms^{-1}

an open blocker is added to both the open states of the Markov model given in Fig. 14.6. By following our usual procedure, we find that

$$\left(o + o^*\right)_{\mu,d} = \frac{1 + \mu\frac{k^d}{k^u}}{\frac{k_{ob}}{k_{bo}}\left(1 + \mu\frac{k^d}{k^u}\right) + \frac{k_{oi}}{k_{io}} + \left(1 + \mu\frac{k^d}{k^u}\right)\left(1 + \frac{k_{oc}}{k_{co}}\left(1 + \beta/\alpha\right)^3\right)}.$$

The associated mean open time is given by

$$\tau_{o,\mu,d} = \frac{\mu k^d + k^u}{\mu k^d\left(k_{oc} + k_{ob}\right) + k^u\left(k_{oc} + k_{oi} + k_{ob}\right)}. \tag{14.19}$$

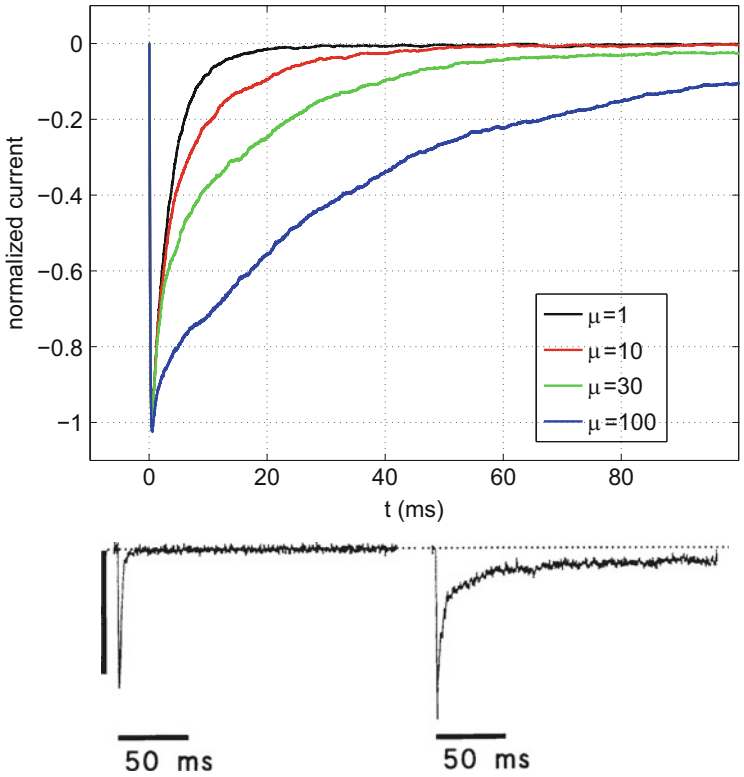

Fig. 14.8 Currents computed using the Markov model including the burst mode (see Fig. 14.6). *Top panel*: Current for $\mu = 1,\ 10,\ 30,\ 100$. Each trace is an average of 10,000 Monte Carlo runs and the current is computed by $I = g_{Na}P_o(v - V_{Na})$, with the transmembrane potential at $v = 0$ mV. The currents are normalized so that the wild type current peaks at -1. Here $V_{Na} = 45$ mV and $g_{Na} = 1\,\text{mS/cm}^2$. The lower figures are from Bennett et al. [2]

Table 14.4 Probabilities and expected values of the transmembrane potential for open and non-conducting states for increasing values of the mutation severity index μ

μ	$1000 \times \pi_o$	π_n	E_o	E_c
1	0.05738	0.99994	−53.2	−84.9
10	0.08435	0.99992	−26.1	−84.9
30	0.12109	0.99983	−8.3	−84.9
100	0.22305	0.99978	10.5	−84.9
30+OB	0.05490	0.99995	−57.0	−84.9

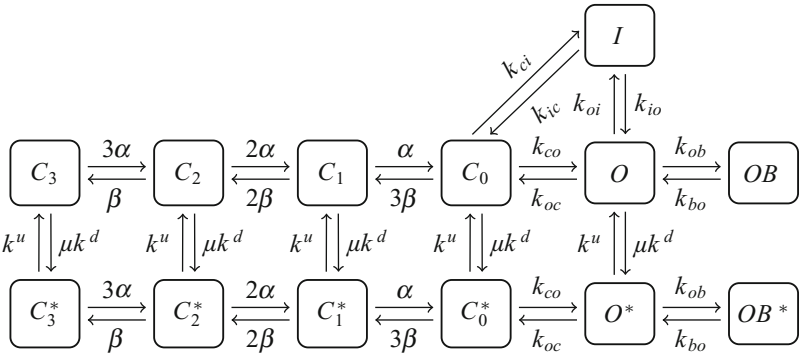

Fig. 14.9 Markov model of the mutant sodium channel with a blocker associated with the open states. The model consists of the states O, I, OB, C_0, C_1, C_2, and C_3 of the normal mode and $OB^*, O^*, C_0^*, C_1^*, C_2^*$, and C_3^* of the burst mode (*lower part*). The drug is characterized by the two parameters k_{bo} and k_{ob}

We now want to tune the drug characterized by the two parameters k_{ob} and k_{bo} such that

$$\left(o + o^*\right)_{\mu,d} \approx \left(o + o^*\right)_{wt}$$

and

$$\tau_{o,\mu,d} \approx \tau_{o,wt},$$

where the subscript *wt* denotes wild type values. As above, we have two equations for the two unknowns k_{ob} and k_{bo} and the solution is given by

$$k_{ob} = (\mu - 1)\,\frac{k^d k^u k_{oi}}{\left(k^u + \mu k^d\right)\left(k^u + k^d\right)} \tag{14.20}$$

and

$$k_{bo} = A^{-1} k_{ob}, \tag{14.21}$$

where

$$A = \frac{k_{oi}}{k_{io}} k^u k^d \frac{\mu - 1}{\left(\mu k^d + k^u\right)\left(k^d + k^u\right)}. \tag{14.22}$$

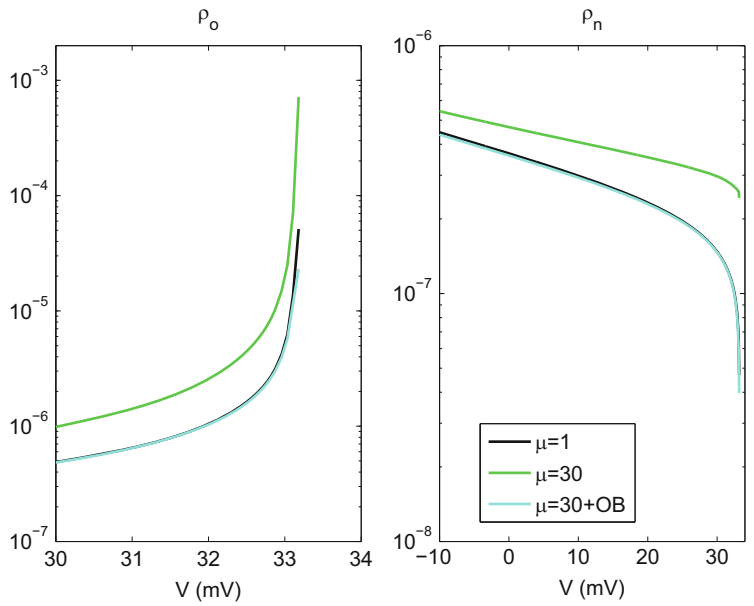

Fig. 14.10 Probability density functions for the wild type, the mutant ($\mu = 30$), and the mutant in the presence of the open blocker. The subscripts o and n refer to open and non-conduction states, respectively, where the states are shown in Fig. 14.9

So we obtain

$$k_{bo} = k_{io}. \tag{14.23}$$

We note that the formulas for the optimal open blocker for the Markov model given in Fig. 14.9 are exactly the same as for the open blocker of the prototype Markov model given in Fig. 14.2.

In Fig. 14.10, we show the probability density functions of the wild type, the mutant (using $\mu = 30$), and the mutant case where the optimal open blocker is applied. The blocker repairs the effect of the mutation and the same effect is seen in Fig. 14.11 where the currents are given; the open blocker removes the late sodium current.

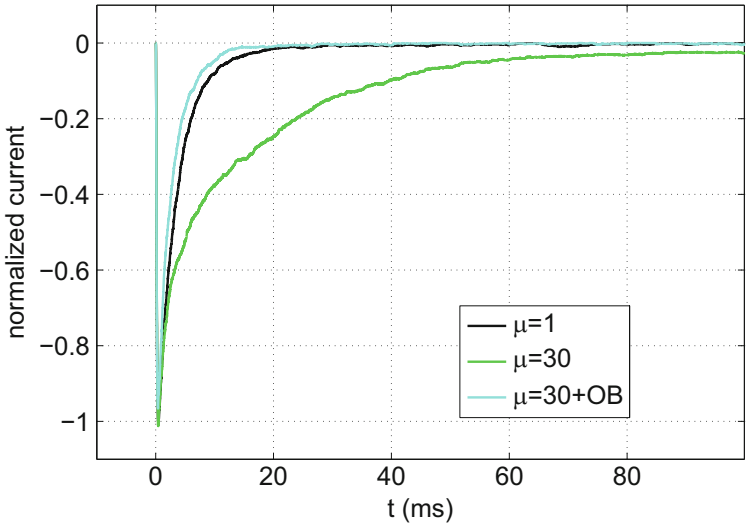

Fig. 14.11 Currents computed using the Markov model given in Fig. 14.9 for the wild type, the mutant ($\mu = 30$), and the mutant in the presence of the open blocker

14.8 Notes

1. The burst mode is discussed by Bennett et al. [2] and modeled in the paper by Clancy and Rudy [14].
2. The form of the model illustrated in Fig. 14.6 is taken from Clancy and Rudy [14], but the functions and parameters of the model are not taken from their paper.
3. As mentioned above, the introduction of a burst mode is a convenient way of modeling the effect of certain mutations. The notion that gating may enter various modes has been considerably extended and studied in the papers by Chakrapani et al. [10–12] and by Ionescu et al. [37]. In the recent paper by Siekmann et al [83] the concept of modal gating is studied and a method for detecting mode changes based on single channel data is developed.